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EXAMINER	
LIU, SAMUEL W	
ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 08/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,215	SKEIKY ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE f this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *17-26 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,27-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary amendment filed 12 March 2002 and the response to the restriction requirement filed on 27 June 2002 (Paper NO: 11) have been received and entered. Applicants' claim for the benefit of U.S. provisional application, SN 60/158585 has been acknowledged. Applicants' response to the restriction requirement with traverse has been fully considered. Applicants argue that the claims of Groups I-III can be examined together without undue burden to the examiner. The argument is unpersuasive because the three Groups are patently distinct from one another (see the reasons stated in the restriction requirement).

Claims 1-31 are pending. Claims 17-26 and 30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Thus, Claims 1-16, 27-29 and 31 are examined in this Office action.

Drawings

The drawing (Figures 1-9) filed 12 March 2002 is acceptable subject to correction of the informalities indicated on the attached "Notice of Draftperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

The following is the information on how to effect drawing changes.

1. New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the

application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

In addition, Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in abandonment of the application.

Specification/Claim/Objections

The disclosure is objected to because of the following informalities:

In page 2, line 21, the term "DPPD" and "WTI" should be spelled out in full at the first instance of use. The same are "CaMV" and "TMV" at page 12, line 31 and "poly His" at page 20, line 12. See also Claim 1 which recites "DPPD" and "WTI".

In the paragraph bridging pages 4-5, "the term 'Ra12 polypeptide' or 'Ra12

polynucleotides' as used herein refer to the native Ra12 sequence (e.g. SEQ ID NO:3 or SEQ ID NO:4), ..." should be changed to "the term 'Ra12 polypeptide' or 'Ra12 polynucleotides' as used herein refer to the native Ra12 sequence, e.g. SEQ ID NO:4 or SEQ ID NO:3, respectively, ..." (note that SEQ ID NO: 4 is polypeptide and SEQ ID NO: 3 is polynucleotide) for clarity .

In page 6, line 31, "that is at least about 25 to about 50 amino acids or nucleotide" should be changed to "that is a nucleotide sequence encoding at least about 25 to about 50 amino acids". See also "over a region that is 75-100 amino acids or nucleotides" in lines 31-32 at the same page.

In page 9, line3, "a defined ionic strength pH" should be changed to "a defined ionic strength and pH". In page 9, line 4 "and nucleic concentration" should be changed to "nucleic acid concentration". In the same page, line 7, "occupied at equilibrium" should be changed to "hybridized at equilibrium".

In page 13, line 16, "mammalian cell system" should be changed to "mammalian cell lines".

In page 16, lines 28-29, "Ra12 polynucleotide sequence (e.g. SEQ ID NO:4)" should be changed to "Ra12 polypeptide sequence (e.g. SEQ ID NO:4)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 27-29 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length Ral2 polynucleotide sequence (SEQ ID NO:3) as a fusion partner in a expression vector and being enabling for immuno-detection, expression and purification of the fusion polypeptide consisting of the full length SEQ ID NIO:4 polypeptide and a heterologous polypeptide sequence, does not reasonably provide enablement for all polynucleotide variants or polynucleotides encoding polypeptide variants thereof and using the variant polypeptides in facilitating the stable and high yield expression of recombinant heterologous proteins of both eukaryotic and prokaryotic origin.

The instant application has provided a description of constructing the full length Ral2 polynucleotide sequence (SEQ ID NO:3) as a fusion partner in the expression vectors and expression and purification of the fusion proteins thereof, and asserts that the variants (DNA fragments) may also be substantially homologous to a native Ral2 polynucleotide (e.g. SEQ ID NO:3), or a portion or complement thereof (see page 8, lines 20-24). The specification provides no factual evidence that the variant forms of the polynucleotide SEQ ID NO:3 have capacities of facilitating expressions of the fused heterologous proteins which are targeted to be purified in high yield and stable forms.

The instant claim language as written appears to encompass numerous polynucleotide variants encoding the corresponding variant polypeptides. The recitation that a polypeptide variant is a polypeptide that differs from a native Ral2 polypeptide in one or more substitution, deletions, additions and/or insertions, such that the biological activity of the polypeptide is not substantially diminished (see page 15, lines 18-21) does not require that the full length nucleic acid (SEQ ID NO:3) encodes the full length polypeptide sequence (SEQ ID NO:4); but rather

encompasses any nucleic acid sequences comprising either the full length of SEQ ID NO:3 or *any variants*. The specification does not appear to have provided any working examples of any variants with respect to retaining the biological activity as intact Ral2 sequence. Thus, the skilled artisan is required to conduct to undue experimentation for determining which variants of SEQ ID NO:3 would identify nucleic acid SEQ ID NO:3.

In this regard, the application disclosure and claims have been analyzed in the light of the factors summarized in *In re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/ The nature of the invention:

The claims of the instant application set forth that the recombinant nucleic acid molecule comprising **a** Ral2 polynucleotide sequence and a heterologous polynucleotide sequence, wherein the Ral2 polynucleotide sequence hybridizes to SEQ ID NO:3 under stringent conditions (see claim1). In the specification, applicants define that the terms "Ral2 polynucleotide" or "Ral2 polynucleotide sequence" refer to native Ral2 polynucleotide (e.g. SEQ ID NO:3), fragments thereof, or any variants thereof (see page 9, lines 28-30). The present

disclosure, therefore, appears to include any variant polynucleotides of SEQ ID NO:3 and the polypeptide fragments encoded by the polynucleotide variants. The specification recites that a Ral2 variant polypeptide is a polypeptide that differs from a native Ral2 polypeptide in one or more substitutions, deletions, additions and/or insertions, such that the biological activity of the polypeptide is not substantially diminished (see page 15, lines 17-21).

Therefore, the claims as written encompass a broad genus of polynucleotide fragments which encode a broad genus of polypeptide fragments including (*i*) a large number of possibilities in respect to the length of the amino acid sequences (see page 15 , the third paragraph) and (*ii*) a vast number of mutational variants: substitution, additions, deletions, fusion and truncations and structural alterations in any combination of the foregoing mutational types (see lines 18-21of page 15 and lines 4-25 at page 16, and see especially page 9 lines 29-30 where sets forth that Ral2 polynucleotide refers to any variants or fragments). However, the instant application provides no example, guidance and working examples as to structural and functional characterization of these variant polypeptides encoded by SEQ ID NO:3 polynucleotide and the corresponding polynucleotide variants.

The specification sets forth that polypeptide variants preferable exhibit at least 95%-70% sequence identity to the full length SEQ ID NO:4 (see page 16, the second paragraph). Making changes up to 30% of a polypeptide sequence does not provide maintaining the same three dimensional structure as the 100% identity over the full length of polypeptide SEQ ID NO: 4. Thus, the instant claim language appears to encompass all possible subsequences of polynucleotide and polypeptide without regarding structure-function relationship. This would create numerous variants (sequences) that are unpredictable on both structure and function. As

stated in the specification, the advantage of using the Ral2 polypeptide in the expression vector relies on the Ral2 being present as a soluble protein throughout the purification process and on high yield production of the Ral2 protein (see page 4, the last paragraph). Since the folds of the variant polypeptides are not invariable, the variants inherited in the current claim language would render the claims so broad that the scope of claims is beyond of the scope of enablement.

As stated above, the claims of the current application are directed to numerous variants of polynucleotide fragments and the polynucleotide encoded polypeptide fragments. Of them, some would be nonfunctional, absent factual evidence to the contrary.

There is insufficient guidance as to which amino acid residue within the polypeptide can be deleted, substituted and whether the resulting polypeptide would maintain the same structure as SEQ ID NOs: 4 protein that readily fold and is soluble during purification process. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Given the lack of sufficient guidance and working examples, predicting what changes can be made to polynucleotide that encode the polypeptide or the amino acid sequence of SEQ ID NO: 4 that after substitution, deletion, insertion and other structural modification will retain the same structure as SEQ ID NO: 4 is unpredictable.

The current application discloses only the Ral2 full length nucleotide sequences (SEQ ID NOs: 3) and the polynucleotide encode polypeptides (SEQ ID NOs: 4). Therefore, one of ordinary skill in the art cannot envision all the contemplated amino acid sequence possibilities

recited in the instant claims. Consequently, conception in the above cases cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

(2) The state of the prior art:

The current invention recites hybridization of the Ra12 polynucleotide to SEQ ID NO;3 under stringent condition (see Claim 1) and the Ra12 polynucleotide refers to ant variants (see page 9, line 29-30) which include any fragments generated via substitutions, insertion, deletion as mentioned in the foregoing. Since the variants are highly unpredictable, the stringent hybridization condition for each variant is highly variable. It has been known that one nucleotide mismatch of polynucleotide causes approximately 1 °C alteration of thermal melting point (T_m) of hybridization (see Adams R. L. P. et al (1986) "The biochemistry of the nucleic acid" page 469, Chapman and Hall, London)

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify any biological active fragment (either the polynucleotide or the polypeptide) for its use, one of ordinary skill is required to perform undue experimentation in order to probe suitable T_m for hybridization using each selected polynucleotide variant, and to determine its use in the expression vector construction.

Additionally, Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Given the lack of

sufficient guidance and working examples, predicting what changes can be made to the polynucleotide sequence (SEQ ID NO:3) so that the amino acid sequence (SEQ ID NO: 4) that after substitution, deletion, insertion and/or modification will retain the same structure as SEQ ID NO: 4 is unpredictable. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid can be deleted or substituted requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure.

The disclosure fails to describe the consequence of the variants, i.e. mutants and their biotechnological use with respect to full length polypeptide, and the common attributes or characteristics that identify members of the genus that encompasses any members of possessing homology ≥ 70% compared to the full length Ra12 (SEQ ID NO:4). Because the genus is highly variant, the specification needs to provide sufficient guidance to support enablement.

(3) The quantity of experimentation necessary:

In the absence of working examples with regard to the numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and making variants which have desirable biological activities.

(4) The unpredictability of the art:

Because of the claimed polynucleotide encompasses numerous sub-sequences (with respect to SEQ ID NO:3) encoding numerous polypeptide fragments (with respect to SEQ ID NO:4) are highly variant, the invention is unpredictable (see the foregoing statement) in the absence of factual indicia to the contrary

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a protein-engineer or a cell biologist with several years of experience in molecular biology, biochemistry, and protein manufacturing as well as knowledge in mutagenesis and bacteriology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly high level of skill is needed for the skilled artisan in order to identify sequence derived from Ral2, construct the fusion polypeptide with the identified sequence, and test for its ability of facilitating stable and high-yield expression of the downstream interest protein.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 27-29 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite as to the recitation "wherein the Ral2 polynucleotide sequence hybridizes to SEQ ID NO:3 under stringent conditions". Note that the said Ral2 polynucleotide refers to any fragments or any variants of Ral2 polynucleotide sequence. The recitation is not apparent as to whether or not any variants fragments hybridize under the same stringent condition which is employed for the full length SEQ ID NO:3 polynucleotide sequence. Also, the recitation "the recombinant nucleic acid molecule comprising a Ral2 polynucleotide" refers to that the recombinant molecule comprising any fragments of Ral2 polynucleotide sequence; this would render the claim out of scope of the present invention since it encompasses any SEQ ID NO:3-derived polynucleotide fragments. Claim 1 is unclear as to the recitation "wherein the aRal2 polynucleotide sequence hybridizes to SEQ ID NO:3"; does the claimed Ral2 polynucleotide therein refer to an antisense strand of the full length SEQ ID NO:3 or any fragments of the full length SEQ ID NO;3 which hybridize? The dependent claims are also rejected, because they inherently these deficiency.

Claim 7 is indefinite in the recitation as to "at least about 30 nucleotide"; it is ambiguous regarding what are encompassed in these limitations. The recitations appear to set "±" parameter on the end of the nucleotides. The recitation, therefore, would result in a vague and unpredictable upper limit for selecting length of nucleotide sequence. See also Claims 8 and 9.

Claim 27 is indefinite as to the recitation "... is encoded by a Ral2 polynucleotide sequence that hybridized to SEQ ID NO:3 under stringent conditions", since "a Ral2 nucleotide

sequence reads on any pieces of Ral2 polynucleotide. The recitation as written, therefore, would render the claim out of scope of the present invention since it encompasses any SEQ ID NO:3-derived polynucleotide fragments. The dependent claims are also rejected.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: screening the recombinant clones and selecting selection positive clone(s) for further protein purification. Note that the identification of positive clone(s) prior to purification step is necessary and essential.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claims 1, 3, 7-9, 12-16, 27, 29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Reed, S. G. et al. (US Patent NO: 6350456).

Reed et al disclose a DAN fusion molecule encoding a fusion protein which consists of a polypeptide that is derived from *M. tuberculosis*, e.g. Ral2 polypeptide (see columns 2-3 and 12,

SEQ ID NO:4 that is the DNA sequence of Ra12 polypeptide (column 4) and SEQ ID NO:66 that is the amino acid sequence of Ra12 (columns 6 and 91), see also column 11, lines 2-12) and the heterologous sequence(s), as applied to Claim 1, 7-9, 12-13 and 27 of the instant application. Also, Reed et al. teach an operable promoter of an expression vector for the fusion protein production (see columns 12 and 15, and column 17, lines 1-17) in the host cell, e.g. *E.coli* (see column 15, lines 40-52), as applied to Claims 14-16, 29 and 31 of the instant application. Additionally, Reed et al. teach a peptide linker sequence being employed to separate the first and the second polypeptide by a distance sufficient to ensure that each polypeptide folds into its ternary structure (see column 16, lines 11-34), as applied to Claim 3 of the instant application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 7-9, 12-16, 27-29 and 31 are rejected under 35 U.S.C. 103(a) as being obvious over Reed, S. G. et al. (US Patent NO: 6350456), taken with Madsen, S. M. et al. (US Pat. NO: 6133023) and Burrows, G. G. et al (US Pat NO:6270772).

Reed et al. teach a DAN fusion molecule encoding a fusion polypeptide containing a polypeptide derived from *M. tuberculosis*, e.g. Ral2 polypeptide and the heterologous polypeptide(s) (see columns 2-3 and 12, SEQ ID NO:4 that is the DNA sequence of Ral2 polypeptide at column 4, SEQ ID NO:66 that is the amino acid sequence of Ral2 at columns 6 and 91, and column 11, lines 2-12), as applied to Claim 1, 7-9, 12-13 and 27 of the instant application. Also, Reed et al. teach an expression vector for the fusion protein production under control by an operable promoter (see columns 12 and 15, and column 17, lines 1-17) in the host cell, e.g. *E.coli* (see column 15, lines 40-52), and teach a peptide linker sequence (see column 16, lines 11-34), as applied to Claims 3, 14-16, 29 and 31 of the instant application.

However, Reed et al. do not teach cleavage of the hybrid (fusion) polypeptide and an affinity tag linking to the fusion polypeptide.

Madsen et al. teach an expression vector for a fusion protein wherein a portion of the fusion polypeptide is derived from *M. tuberculosis* (see columns 4 and 11) and teach that the expression vector contains the cleavage site for a peptidase (see Example 6), as applied to Claim 4 of the instant application. Also, Madsen et al. teach an affinity tag for the expression vector (see column 40, lines 1-3), as applied to Claim 5 and 28 of the instant application.

Further, Burrows et al. teach the peptide linker of a expression vector contains a cleavage site for a specific protease action (se column 6, lines 1-3 and column 15), as applied to Claim 4 of the instant application.

One of ordinary skill in the art would have combined the teachings of Reed et al., Madsen et al. and Burrows et al. for the following advantages: (*a*) high yield expression of the interest protein as a partner of the fusion construct with secretable characteristic as taught by Madsen et al. (See column 7, the first paragraph); (*b*) production of appropriately folded protein employing a peptide linker sequence that separates the first and the second polypeptide by a distance sufficient to ensure that each polypeptide folds into its ternary structure; and (*c*) selective proteolytic cleavage of the hybrid protein to release intact protein of interest, as taught by Reed et al. and Burrows et al.

Given the above motivation one skilled in the art would have combined the teachings of Red et al. Madsen et al. and Burrows et al. as to constructing an expression system wherein a fusion partner is a polypeptide derived from *M. tuberculosis* whose role is to foster the downstream interest protein expression in high yield and in a stable (soluble) form having desirable biological activities.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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August 23, 2002